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Genes on the X Chromosome Are Important in Undiagnosed Mental Retardation

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The clinical genetic diagnosis was reviewed in 429 subjects with intellectual disability in the Australian Child and Adolescent Development (ACAD) study of behavioural problems. With minor differences, the overall "general distribution by causation" was similar to that to that found by the Consensus Conference of the American College of Medical Genetics in 1995. There was a significant male excess in the whole series which was shown to reside in those with "autism," those with undiagnosed nonsyndromic mental retardation (NSMR) and those with X-linked monogenic disorders. It is argued that a substantial proportion of undiagnosed NSMR is caused by genes on the X chromosome. Some of the practical problems of assigning individuals to diagnostic groups are discussed. Am. J. Med. Genet. 92:57–61, 2000. © 2000 Wiley-Liss, Inc.

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INTRODUCTION

An excess of males over females in a proportion of about three to two has been noted in community surveys of the mentally subnormal for over a century. Originally, the popular explanation (strongly supported by Langdon Down), was that this was due to "the greater size of the male head, exposing the infant to greater difficulties and injuries during labour" [Ireland, 1900]. Later, the male excess was attributed to bias of ascertainment, with males more likely to come to the attention of the authorities because affected males "are more difficult to manage in the house than affected females" [Dewey et al., 1965] or because parents seek assistance more frequently for boys than for girls because of different expectations for males [Nance and Engel, 1972]. Any special contribution by genes on the X chromosome was specifically denied by L.S. Penrose, who, in his textbook, stated that "in general genes on the X chromosome do not play any greater part in the causation of mental defect than might be supposed from the fact that there are 22 autosomes to one sex chromosome in man" so that, "the conclusion may be drawn that there is no outstanding tendency for sex-linked genes to influence the genetics of mental deficiency." [Penrose,1963].

In the late 1960s and 1970s, evidence to contradict Penrose began to emerge from quite separate studies. First, there were increasing reports of large families in which mental retardation was segregating in an undoubted X-linked fashion [Lehrke, 1972, 1997], and second, in independent surveys a marked excess of brothers with mental retardation was found compared to affected sisters [Turner and Turner, 1974; Herbst, 1980]. Beyond these were the clinical and cytogenetic delineation of fragile X syndrome and the identification of its underlying dynamic mutation, the mapping of several well-recognised syndromes to segments of the X chromosome and the description of many new forms of X-linked mental retardation (XLMR). A recent review lists 178 such conditions [Lubs et al., 1999]. Many of us believe that mutant genes on the X chromosome contribute disproportionately to the sum of mental retardation.

Recently, as part of the Australian Child and Adolescent (ACAD) study, we reviewed the diagnosis in 429 children and adolescents with intellectual handicap living in the community. We were interested to see if after all the known X-linked disorders were removed there was continuing evidence for X-linked genes in the aetiology of mental retardation in the remainder.

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MATERIALS AND METHODS

The ACAD study is a representative, community-based, longitudinal study of behaviour in young people with intellectual disability [Einfeld and Tonge, 1996a,b]. Subjects were first recruited into the study and assessed in 1990/91. A second assessment was made 5 years later and this included the present diagnostic review.

The group consisted of 429 subjects age 10–24 years; there were 249 males and 180 females. In 280 (65%) the IQ had been measured as less than 50, in 114 (27%) as over 50, and in 35 (8%) no measurements were available. Initial contact was made by telephone. In 74 subjects the diagnosis was clear-cut (e.g., trisomy 21 or other documented chromosomal abnormality) and accepted with or without a case record review. The remaining 355 subjects were seen personally by one or more of three clinical geneticists at special clinics, in their own homes or other places of residence. Details of past and family histories obtained over the telephone were confirmed and extended, a clinical examination carried out, photographs taken, and further investigations arranged if deemed appropriate.

The subjects were then sorted into three main categories. Category A contained those in whom a firm causal diagnosis had been established. Category B contained those who fit into well-recognised descriptive clinical groups without a known aetiology, such as cerebral palsy, epilepsy, and autism. Category C contained those where no diagnosis had been made. Each category was divided into clinical subgroups as shown in Table I. The subjects in Category C were divided into those where the only manifestation was mental retardation and those with an associated abnormality, the significance or relevance of which to mental retardation was unclear. The former group was referred to as nonsyndromic mental retardation (NSMR) and the latter as nonsyndromic mental retardation plus (NSMR plus).

A family history was accepted as positive if there were one or more first-, second-, or third-degree relatives with comparable mental retardation. A simple chi-square test, using Yate's correction, was used to assess the significance of the sex ratios on the expectation of equal numbers of each sex.

RESULTS

In Category A the chromosomal group contained 91 subjects or 21% of the whole series (Table I). Of these, 63 (15% of the whole series) had Down syndrome; all were trisomy 21 except for one with a de novo 21/21 translocation. There were six subjects with partial chromosomal deletions (2q-,4q-,5p-,8q-,9p-,18p-), one ring 18, three with partial duplications (2p+,10q+,13q+), one with an unbalanced (3;5) translocation, two with sex aneuploidy (49,XXXXY, XYY/XY mosaic), and two with supernumerary markers, one of which was unidentified and the other was inv dup (15). There were three with Prader-Willi syndrome, three with Angelman syndrome, two with Williams syndrome, and one with velo-cardio-facial syndrome. There were also three members of a family with a cryptic translocation, one of whom had Pitt-Rogers-Danks syndrome from a 4p16.3 deletion and the others a 4p16.3 duplication leading to overgrowth and mental retardation [Partington et al., 1997].

TABLE I. Distribution of Subjects by Category, Diagnostic Group, and Sex

Category/group	N	(%)	M	F	χ^2	~*P*
A/known diagnosis	191	(45)	98	93	0.05	0.8
Chromosomal	91	(21)	35	56	4.4	0.04
Down syndrome	63	(15)	26	37	1.6	0.25
Other	28	(7)	9	19	2.9	0.08
Monogenic	31	(8)	22	9	4.6	0.03
Autosomal	13	(3)	8	5	0.31	0.55
X linked	18	(4)	14	4	4.5	0.03
Environmental	69	(16)	41	28	2.1	0.15
Prenatal	12	(3)	6	6	—	—
Perinatal	36	(8)	21	15	0.69	0.4
Postnatal	21	(5)	14	7	1.71	0.18
B/descriptive diagnosis	119	(28)	75	44	7.56	0.006
Neurologic	75	(18)	38	37	—	—
Structural CNS	26	(6)	15	11	0.35	0.55
Cerebral palsy	28	(7)	10	18	1.75	0.19
Epilepsy	21	(5)	13	8	0.76	0.33
Syndromic	19	(4)	15	4	5.26	0.02
Recognized	7	(2)	6	1	2.3	0.12
Suspected	12	(3)	9	3	2.1	0.15
Autism	25	(6)	22	3	13.0	<0.0005
C/unknown diagnosis[a]	119	(28)	76	43	8.61	0.003
NSMR plus	36	(8)	24	12	3.36	0.07
NSMR	83	(19)	52	31	4.82	0.03
All	429	(100)	249	180	10.78	0.002

[a]See text regarding nonsyndromic mental retardation (NSMR) and NSMR plus.

The monogenic group comprised four with autosomal recessive disorders (MPS III, Smith-Lemli-Opitz syndrome, "true" recessive microcephaly with consanguineous parents, congenital muscular dystrophy). There were nine with autosomal dominant conditions (four with tuberous sclerosis, two with myotonic dystrophy, and one each with Stickler syndrome, Robinow syndrome, and autosomal dominant microcephaly observed and measured in three generations). The rest were X-linked; four with fragile X syndrome, four from families with NSXLMR, one of which (MRX17) had been mapped to the X chromosome [Gedeon et al., 1994], three with Rett syndrome, two brothers with ATR-X previously described as Smith-Fineman-Myer syndrome [Ades et al., 1991], one each with Lowe syndrome, Borjesson-Forssman-Lehman syndrome, adrenoleukodystrophy, Duchenne muscular dystrophy, and Pelizaeus-Merzbacher disease.

Those in whom environmental or accidental causes were deemed responsible are shown in Table I subdivided into prenatal, perinatal, and postnatal groups. In the prenatal group, five subjects had had prenatal viral infections (three CMV and two rubella); there were three sibs where the mother had PKU and in one each the retardation was attributed to: maternal severe physical trauma; hydantoin and morphia overdose with respiratory failure; hyperpyrexia; and repeated intrauterine transfusions for severe Rh disease.

In the perinatal group the causes were often multiple, with prematurity associated with intraventricular haemorrhage or hypoxic-ischaemic encephalopathy being the most common. The postnatal group included pyogenic meningitis (five), encephalitis or encephalopathy (six), head injury (two), and nonaccidental injury (two).

Category B was subdivided into descriptive clinical groups. The neurologic group comprised those in whom the primary manifestation was a structural abnormality of the central nervous system (CNS). These included hydrocephalus with and without a neural tube defect (seven), nonsyndromic microcephaly (five) and macrocephaly (three), brain tumours (two), cerebellar agenesis (two), and one each of lissencephaly and holoprosencephaly. The cerebral palsy group contained those where the predominant disability was spasticity with or without athetosis where no cause had been identified. The commonest condition was spastic quadriplegia with or without seizures (16), choreo-athetosis (five), and hemiplegia (seven). In the group with epilepsy, various forms of seizures were the main source of disability. The seizures were often complex and all were difficult to control. Three subjects had Lennox-Gastaut syndrome and one Landau-Kleffner syndrome.

There was a small syndrome subgroup. This included seven with recognised syndromes (De Lange (two), Kabuki (two), and one each with Rubinstein-Taybi and Sotos syndrome and one with CHARGE association). There were another 12 in whom the clinical manifestations strongly suggested a syndrome, but none had been identified and so were labelled as provisionally unique.

The group of young people with autism had been diagnosed by psychiatrists and had histories and behaviour which, to us, were consistent with the diagnosis. All were isolated cases except for one boy who had a similarly affected older brother.

Category C contained those that fit into no descriptive clinical group and in whom no cause was apparent. In two-thirds of these mental retardation was the only clinical manifestation (NSMR), but in the rest each individual had at least one other clinical abnormality whose relevance to their mental retardation was uncertain. These included mild to moderate hearing loss (four subjects), moderate short stature (three), a degree of macrocephaly (two) or microcephaly (three) with head circumferences of between 2 and 3 standard deviations from their respective means, occasional seizures (three), congenital heart disease (two), hypernasal speech (two), and one each of cleft palate, brachycephaly, camptodactyly, arthrogryposis, congenital dislocation of the hip, tremor, hypotonia, and localised hypomelanosis. In seven the facial appearance was abnormal (accepted if at least two of the three clinical geneticists agreed).

Sex Distribution

The sex distribution of the series is also shown in Table I. In the sample as a whole (Table I, bottom line) there was a highly significant excess of males, with a male-to-female ratio of 1.38 to 1. When the series was divided into categories there was no significant male excess in Category A. In the subgroups of this category there was, as expected, a male excess in the X-linked, monogenic disorders. A small but unexpected (and unexplained) female excess was found in the chromosomal group.

In Category B there was a clear male excess, with an M/F ratio 1.7 to 1. This was, as expected, accounted for mainly by the autistic patients. In Category C there was also a male excess (M:F ratio 1.77:1) somewhat more significant in those with NSMR than NSMR plus.

Family History

No family history was obtained in 53 subjects or 12% of the whole series with a range of from 6–25% across the various groups. A positive family history was obtained in 20% of the whole series. The rate was highest in the monogenic group (67%) and high in those with NSMR (30%).

DISCUSSION

The allocation of most of the subjects to the various categories, groups, and subgroups was straightforward, but in a substantial minority more or less arbitrary judgments had to be made. Some of these were easy and of little consequence, such as whether to include the cases of Prader-Willi, Angelman, and Williams syndrome in the chromosomal rather than the syndromic group or whether nonsyndromic macro- and microcephaly should be defined by head circumferences 3 rather than 2 standard deviations from the means for the appropriate age and sex. But others were more difficult and of greater consequence. It was decided to accept a diagnosis of nonsyndromic X linked mental retardation (NSXLMR) if the only manifestation was

mental retardation which was present in two or more second- or third-degree relatives of the propositus connected through females with no evidence of direct male-to-male transmission; furthermore, if females were affected they would be less severely affected than males. There were considerable subjective and arbitrary decisions in the assessments of the aetiological importance of perinatal events and of encephalitis and encephalopathy. There were also problems in deciding whether the clinical findings in a particular subject were coincidental or sufficient to warrant the label of a provisionally unique syndrome [Cohen, 1982].

Others in this field must have had to make the same kinds of arbitrary decisions, but would not necessarily have reached the same conclusions. This is one factor which makes comparisons between surveys of the intellectually handicapped difficult. Other factors are differences in the populations studied (a selected age group; only those with severe mental retardation; patients of a particular clinic, institution or service; those living in the community), differences in methods of study (statistical reports and case records only; clinical examination) and differences in the objectives (the need for community services; the fraction of cases theoretically preventable; the effects of modern perinatal care; the value of routine cytogenetic or radiological investigations). These problems have been addressed in detail by Curry et al. [1997] and Roeleveld et al. [1997].

Nevertheless, broad comparisons between surveys are possible, as shown by the consensus conference held under the auspices of the American College of Medical Genetics in 1995 [Curry et al., 1997]. Having acknowledged the problems of comparisons, the conference put forward "a general distribution by causation" based on a review of nine surveys carried out from 1977–1994. These are shown in Table II together with the frequency of Down syndrome in some more recent surveys and the present data slightly rearranged from Table I to facilitate comparison. It can be seen that the frequencies match well in most groups except for slightly fewer structural CNS and endocrine/metabolic abnormalities in our series. We conclude that, overall, the present series is representative of the mentally retarded population and that our findings can be generalised.

TABLE II. Comparison of the Causes of Mental Retardation in the Present Series With the Ranges Published by the Consensus Conference [Curry et al., 1997] and Others

Category/group	Present series[a] %	Curry et al., 1997 % range
Chromosome abnormalities	21	4–28
Down syndrome	15	12.9–16.1[b]
Recognisable syndromes	2	3–7
Provisional unique syndromes	3	1–5
Known monogenic conditions	7	3–9
Structural CNS abnormalities	6	7–17
Complications of prematurity	8	2–10
Environmental/teratogenic	8	5–13
Metabolic/endocrine	0	1–5
Unknown	46	30–50
Male/female ratio	1.38	1.35–1.4[c]

[a]Data regrouped from Table I to facilitate comparison.
[b]Wellesley et al. [1991], Matilainen et al. [1995], Hou et al. [1998], Cans et al. [1999].
[c]As for fn. b except for Matilainen et al. [1995].

Table II also shows the male/female ratios of several recent series. The consistency of the male excess over 100 years is remarkable. During this time there have been vast social changes in the Western world, including a declining birth rate, a fall in infant mortality and far less severe acute and chronic disability from accidents, infections, and malnutrition. There have been improvements in general living standards, wider public education, and an increased life expectancy for all. A priori, this suggests that the consistent male excess found in mental retardation is inherent in the constitution of the male and so is likely to be genetic, with the genes located on the X chromosome.

Our review of the distribution of the male excess within the series (Table I) shows that it resides in autism, the known monogenic X-linked disorders and in those with undiagnosed NSMR. Little more needs to be said about the monogenic disorders. In the nonsyndromic group the male excess points to genes on the X chromosome. Some further support for this view comes from the virtual absence of published reports of unequivocal autosomal dominant or recessive forms of NSMR. This is in marked contrast to nonsyndromic deafness, where autosomal dominant and recessive forms far exceed those which are X-linked.

Autism is a special case. Although a male excess is regularly reported in surveys of autism and there is an increased recurrence risk for sibs, the characteristic pedigrees of monogenic X-linked disorders with affected male maternal uncles and cousins related through sisters are not found. This indicates that autism and NSXLMR have quite different underlying causes.

If the male excess in NSMR is, as argued here, due to genes on the X chromosome, it is not yet clear whether the affected males represent isolated cases of types of NSXLMR already described and mapped or whether several more new entities are to be discovered. This should become clearer as more genes for NSXLMR are cloned. However, a proper assessment of the full contribution of genes on the X chromosome to mental retardation is compounded by their expression in females. From clinical experience with NSXLMR and by analogy with fragile X syndrome it could be that 50% of females who carry genes for XLMR will have some degree of intellectual handicap.

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